PHARMACOLOGICAL-KINETIC RESEARCH AND STUDY OF AN ACUTE TOXICITY OF THE PREPARATION PYRACIN-RG IN AMPULES

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Nowadays, during an early diagnostics and treatment of a number of diseases, a special attention is paid to pathologic conditions that are linked to the lack of zinc microelements and vitamins of group B in an organism. Multiple researches show that zinc participates in almost all stages of cell formation. A special interest towards zinc is linked to its part in nucleic exchange, processes of transcriptions, stabilization of nucleic acids, proteins, and specially components of biologic membranes, and also in the exchange of a number of vitamins. Zinc has been found in composition of over 300 ferments. A uniqueness of zinc bio-efficiency is that none of elements is contained in such a number of ferments and carries out so much different physiological functions. Diversity of physiologic functions of zinc is defined by combinations of this microelement with different vitamins. Particularly, a correct combination of zinc and pyridoxine provides a maximum efficiency of both components, and also a refill of a deficit in an organism that is an urgent solution for a number of problems of maternal diseases, growth and development of a child, maturing, metabolism.

Keywords: early diagnostics, zinc microelements, vitamins of group B, biologic membranes

Thus, researches of recent years point out a special attention towards therapeutic combinative effect of pyridoxine and zinc. During the development and introduction of new medications into medical practice, pharmacological researches play a special part, as their results allow one to receive accurate quantitative data on absorption, distribution, metabolism, and extermination of a medicine, and also show a correlation dependence of pharmacologic activity and pharmacologic parameters of a medication [1, 2].

Pyracin is a complex solution of zinc microelement with pyroxidin. Due to pharmacologically rational doze of the preparation components, Pyracin has a wide range of therapeutic effect. Studies of metabolic activity of the preparation show that Pyracin has hypolipidemic and anti-atherosclerotic activity, decreases contents of cholesterol in periphery blood, general lipids, treglycerides, lipoproteins of low density, products of peroxide oxidation of lipids, increases contents of lipoproteins of high density and phospholipids. Under sugar diabetes with hyperlipidemia, the preparation decreases contents of glucose, pyruvate, and lactic acid in blood. Besides, the preparation is widely used in treating dermatologic-venereologic pathologies in terms of skin displays that are linked to a deficit of zinc (vitiligo, inflammatory and seborrheic alopecia, pustular and phegmonous acne, acrodermatitis enteropathica, difficult-to-heal skin ulcers) [3].

Objective: pharmacologic kinetic research of acute toxicity of the medical preparation «Pyracin-RG», injection solution 0,25%, produced by Joint Enterprise «Remedy Group», Tashkent, Republic Uzbekistan.

Finding a preparation dose for pharmacologic kinetic research was carried out via studying an acute toxicity of «Pyracin-RG». The research has been implemented on white pedigreeless mice of both sexes of mass 18–20 g, 6 animals per a group, total of 24 mice have been used.

The tested solution was introduced to animals one time hypodermically in dose: 15; 2; 22,5; 25 ml/kg.

After a single introduction of the medication, the animals were observed hourly on the day of introduction, 3 times a day on days 2–3 after the introduction, and once a day during the following 7 days of the research. We have examined general condition, behavior, fur pigment, breath, heartbeat, moving activity, and death of the mice.

Under the dose of 15 ml/kg, the first 15 minutes we have been observing breath of increased frequency, grouping, the mice moved slowly, scratched and washed. Under the dose of 20 ml/kg, during the first 45 minutes, a heavy short breath, slow movement, itching, and grouping has been observed. The dose of 22,5 ml/kg led to a heavy short breath, immobility, grouping during the first 1,5 hours, and also strong itching during the first 15 minutes.

Under the dose of 25 ml/kg a strong itching, heavy short breath, immobility, grouping has been observed during the first 2 hours.

Death of animals has not been observed after the introduction of «Pyracin-RG» (Table 1).

Therefore, the preparation does not have a lethal-toxic effect in the studied doses.

Pharmacologic-kinetic parameters of the medication have been estimated according to a quantitative content of zinc in organs and tissues.

43 pedigreeless white male rats of body mass of 180–200 gr have been used in the experiment. A control group has been formed of 3 animals, definition of pyracin in fecal mass has been carried out among 5 animals, and 5 rats have been selected at each checkpoint. The studied preparation was introduces hypodermically to the experiment rats in dose of 5 ml/kg. Tests of blood and organs have

been received in 30 minutes, 1, 2, 3, 4, 6, and 24 hours after decapitation of animals. Fecal masses were also collected once available, as the main criterion of zinc excretion is gastrointestinal tract. Fecal losses of zinc consist of non-absorbed and secreted zinc endogen.

Table 1

Results of defining an acute toxicity of «Pyracin-RG»

Number	Dose (ml/kg)	Number of animals/total dead (units)
1.	15	6/0
2.	20	6/0
3.	22,5	6/0
4.	25	6/0
Lethal $Dose_{50}$ > 25 ml/kg		

Organs, blood serum, and faeces have been analyzed via method of optical-emission spectrometry with inductively-linked argon plasma. 0,500–2,000 of the examined organ have been weighed and transported to teflon autoclaves. 3 ml of nitrous acid and 2 ml of hydrogen peroxide have been added to autoclaves, then they were closed and placed into a facility of microwave dissolution BERGHOF, equipped with the software Speebwave™ MWS-34+. After the dissolution contents of autoclaves were transited into a 50 ml measure retort and have been added up to the mark of 2 % nitrous acid.

Definition of the studied substance has been carried out on optical-emission spectrometer with inductively linked argon plasma Optima-2100 DV (USA). Optimal wave length of the defined channel Zn has been used, with it the element discharges its maximum emission of the absorbed energy. Quantitative content of the studied element Zn in samples was calculated according to the formula (mkg/g):

$$Zn = N \cdot 100/C,$$

where N is a quantity of metal from the graphic (mg/kg); C is a concentration of the studied sample in the prepared solution.

Organs and faeces of rats contain certain amount of zinc. Therefore, via excluding control data from the experiment rats, we find the quantity of zinc that has penetrated them with the preparation (mkg/g).Considering zinc contents in pyracin, we have re-calculated the preparation dose and established its concentration on the studied object. Multiplying the received results by weight of each organ, we have calculated contents of pyracin in an organ, it is shown in Table 2.

Table 2

Quantitative contents of Pyracin in organs in faeces of rats (mkg/organ)

Number	Checkpoints (minutes)						
	30 minutes	1 hour	2 hours	3 hours	4 hours	6 hours	24 hours
1	2	3	4	5	6	7	8
Liver							
1	705,1	1095	30,779	257,28	716,38	756,74	282,67
2	607,4	1072	29,74	287,72	727,79	703,6	343,57
3	584,5	932,6	24,577	346,81	843,02	828,43	288,32
4	570,2	959,4	24,725	347,1	842,18	726,1	308,74
5	537,7	842,9	21,383	340,28	781,25	797,28	298,47
Average	601,0 ± 63,47	980,40 ± 103,9	26,241 ± 3,92	315,84 ± 41,089	782,12 ± 60,398	762,43 ± 50,95	304,35 ± 24,076
Kidney							
1	52,01	56,24	54,758	45,636	83,135	59,157	19,509
2	43,29	40,64	52,353	60,617	94,111	44,23	25,013
3	38,4	44,46	57,745	73,903	125,42	50,717	21,073
4	34,3	43,85	48,650	72,144	107,49	54,716	24,555
5	36,72	56,12	44,479	67,145	113,83	48,852	24,537
Average	40,940 ± 7,007	48,260 ± 7,372	51,5976 ± 5,188	63,889 ± 11,433	104,800 ± 16,565	51,534 ± 5,68	22,937 ± 2,48
Lungs							
1	91,82	15,16	1,327	–	–	–	–
2	121,1	11,34	1,358	–	–	–	–
3	79,09	8,832	0,811	–	–	–	–
4	91,52	11,53	1,132	–	–	–	–
5	110	10,3	1,225	–	–	–	–
Average	98,71 ± 16,69	11,43 ± 2,34	1,171 ± 0,21	–	–	–	–
Lien							
1	2,893	7,259	128,835	22,963	43,625	20,184	7,6677
2	2,252	8,845	109,591	27,706	43,754	32,539	17,309

End of the table 2

1	2	3	4	5	6	7	8
3	4,046	10,39	132,89	30,136	38,11	40,172	12,327
4	3,466	7,617	97,7924	41,746	38,809	31,505	14,075
5	2,757	4,658	81,99	48,852	46,979	29,585	13,111
Average	3,083 ± 0,69	7,754 ± 2,12	110,22 ± 21,28	34,28 ± 10,683	42,255 ± 3,72	30,797 ± 7,16	12,898 ± 3,48
Faeces							
1	1,291	–	–	–	–	125,674	1830,598
2	–	–	12,573	–	–	123,707	1924,699
3	0,627	–	–	–	–	130,456	1794,714
4	1,047	–	14,387	–	–	127,464	1728,33
5	–	–	8,997	–	–	128,44	1742,372
Average	0,988 ± 0,335	–	11,985 ± 2,742	–	–	127,14 ± 2,58	1804,143 ± 78,87
Blood (mkg/ml)							
1	10,794	18,966	20,406	73,628	24,062	3,934	–
2	10,730	19,396	20,600	73,134	24,040	3,848	–
3	10,772	19,246	20,492	73,522	24,084	4,342	–
4	10,622	19,482	20,126	73,780	24,126	4,300	–
5	10,686	19,352	20,642	73,306	24,040	4,256	–
Average	10,72 ± 0,068	19,29 ± 0,18	20,45 ± 0,20	73,46 ± 0,26	24,06 ± 0,02	4,136 ± 0,22	–

According to the received data on the amount of pyracin in rat blood we have carried out calculations of pharmacological-kinetic parameters for the studied preparation in the application Borgia [4, 5]:

T_{max} – period of achieving maximum concentration, minutes;

C_{max} – maximum concentration, mkg/ml;

Period of half-absorption, K ½, minutes;

Clearance, Cl, ml/min;

Area under the curve, AUC;

Average period of hold, MRT (0-∞).

Pharmacological parameters are provided in Table 3.

Table 3

Pharmacological-kinetic parameters for «Pyracin-RG», solution of 0,25 %

Pharmacological-kinetic parameters	Parameter indexes for serum
Tmax, minutes	162,4 ± 0,894
Cmax, mkg/ml	75,123 ± 0,375
$Ka_{1/2}$, minutes	53,801 ± 1,041
$T_{1/2}$, minutes	41,992 ± 0,230
Cl, ml/min	0,0438 ± 0,0004
AUC	22529 ± 732,1
MRT (0-∞)	19,54 ± 0,151

Thus, the received research data of the amount of pyracin in organs and faeces of rats in definite time periods – 30 minutes, 1, 2, 3, 4, 6, and 24 hours after the introduction of medicine in calculations (mkg/g) show its concentration in blood, liver, kidney, lungs tends to decrease in later periods of the experiment in comparison to its earlier periods. On the other hand, concentration of pyracin in lien and faeces tends to increase, obviously, due to the maximum excretion and accumulation of zinc solutions in the studied biomaterials.

The provided research has shown that in 24 hours after the medicine introduction, 72 % of pyracin is removed from rat organism with faeces. In 24 hours after the introduction the medicine cannot be found in an organism. Maximum contents of pyracin in lungs are observed is observed during the first 30 minutes after the introduction, and it is removed in 3 hours. Maximum concentration of pyracin in lien is observed in 2 hours after the introduction, and in 24 hours only 0,05 % of the preparation remains. Maximum content of pyracin in kidney is observed in 4 hours after the introduction. After 24 hours of observation 0,9 % of the preparation remains in kidney. Concentration of pyracin in liver reaches its maximum concentration in 4-6 hours after the introduction, and 1,23 % of the medicine remains in it after 24 hours.

Resume

1. «Pyracin-RG» 0,25 % solution does not lead to death of an animal after a single introduciton.

2. Results of the pharmacological-kinetic research show that a maximum concentration of pyracin in blood serum equals 75, 1,23 mkg/ml, period of achieving it – 2 hours

40 minutes, and period of its half-distribution in blood equals 42 minutes. In 24 hours after the introduction Pyracin cannot be found in blood. 72 % of the preparation is removed from rat organism with faeces.

3. Study of Pyracin distribution dynamics throughout organs has shown that maximum contents of pyracin in lungs is observed is observed during the first 30 minutes after the introduction, and it is removed in 3 hours. Maximum concentration of pyracin in lien is observed in 2 hours after the introduction, and in 24 hours only 0,05 % of the preparation remains. Maximum content of pyracin in kidney is observed in 4 hours after the introduction. After 24 hours of observation 0,9 % of the preparation remains in kidney. Concentration of pyracin in liver reaches its maximum concentration in 4–6 hours after the introduction, and 1,23 % of the medicine remains in it after 24 hours.

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